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⑫

EUROPEAN PATENT APPLICATION

㉑ Application number: 88202139.7

㉑ Int. Cl. 4: A23K 1/17, A01N 43/90,
A61K 31/70, C07D 493/22,
C07H 19/01

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㉕ Prevention of fescue toxicosis in grazing animals.

㉕ There is disclosed a method for the prevention of fescue toxicosis in grazing animals. Fescue toxicosis results from a grazing animal ingesting certain toxins present in or on the grass which can impair growth, reproductive performance, and is sometimes fatal. It has been discovered that the administration of ivermectin or related avermectin compounds is effective in reducing or eliminating the toxic effects of fescue endophyte ingestion.

EP 0 311 195 A2

PREVENTION OF FESCUE TOXICOSIS IN GRAZING ANIMALS

BACKGROUND OF THE INVENTION

5 Tall fescue has good forage quality for grazing animals in that it has adequate crude protein and satisfactory digestability. However, animals often perform poorly on it and suffer from various disorders such as "fescue foot", characterized in rough coats, weight loss, fever, tenderness or loss of hooves and tails and sometimes death; "bovine fat necrosis", characterized in hard masses of fat along the intestinal tract resulting in digestive upsets and difficult births; and "fescue toxicity", also called "summer slump" because of its common incidence in hot weather, characterized in poor weight gain, reduced conception 10 weights and intolerance to heat.

Higher levels of incidence of fescue toxicosis have been observed in fields infected with certain fungi, in particular endophytic fungi (See Schmidt et al. Journal of Animal Science 55 1260-1263 (1982) Hoveland et al. Agronomy Journal 72 pg 375-377 (1980) and Hoveland et al. Circular 270 from Alabama Agricultural Experiment Station, Auburn University, Alabama (1984)). Certain researchers have compared pastures of tall 15 fescue with and without contamination by the fungus Acremonium coenophialum and observed a decrease in performance and weight gains and an increase in typical symptoms of fescue toxicosis in pasture with higher levels of A coenophialum contamination (See Hoveland et al. Agronomy Journal 75 pg 821-824 (1983) and Pedersen et al. New Zealand Journal of Experimental Agriculture 14 pg 307-312 (1986)).

The endophyte infection of tall fescue is very wide spread, and the fungus is found in the fescue seeds. 20 Thus, the fungal infection is carried over from one season to the next and has been found very difficult to eradicate. Current methods of endophyte control to prevent fescue toxicosis require fields to be chemically treated to destroy the fescue and then planted with other crop for 1,2 or more seasons to allow any residual seeds and their fungal contamination to be killed. Then the field must be planted with seeds specially grown to be free of endophyte contamination. Such procedures are obviously very labor intensive and costly and 25 often will exceeds the savings resulting from the elimination of fescue toxicosis from pasture fed animals. Any savings that might result may then be defeated if the field is later reinfected with the fungus. Obviously the economical treatment of fescue toxicosis has long been a goal of breeders and growers of pasture fed livestock.

Ivermectin is a semi-synthetic member of the class of compounds known as avermectins which are 30 macrocyclic esters which have been discovered to be highly potent antiparasitic agents for animals of both endo and ectoparasites. The compounds have further been found to be highly active as an agricultural pesticide and nematocides against insects which parasitize the aerial parts and roots of growing plants as well as stored agricultural products. Avermectin compounds however are not fungicidal and no reports of any fungicidal activity have been found.

35

SUMMARY OF THE INVENTION

This invention concerns the novel and unexpected utility of avermectin compounds, in particular 40 ivermectin, to prevent the effects of fescue toxicosis in animals grazing on tall fescue infected with fungi. Thus, it is an object of this invention to describe such new utility and the avermectin compounds possessing it. A further object is to describe methods of administering such avermectin compounds to grazing animals. Further objects will become apparent from a reading of the following description.

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DESCRIPTION OF THE INVENTION

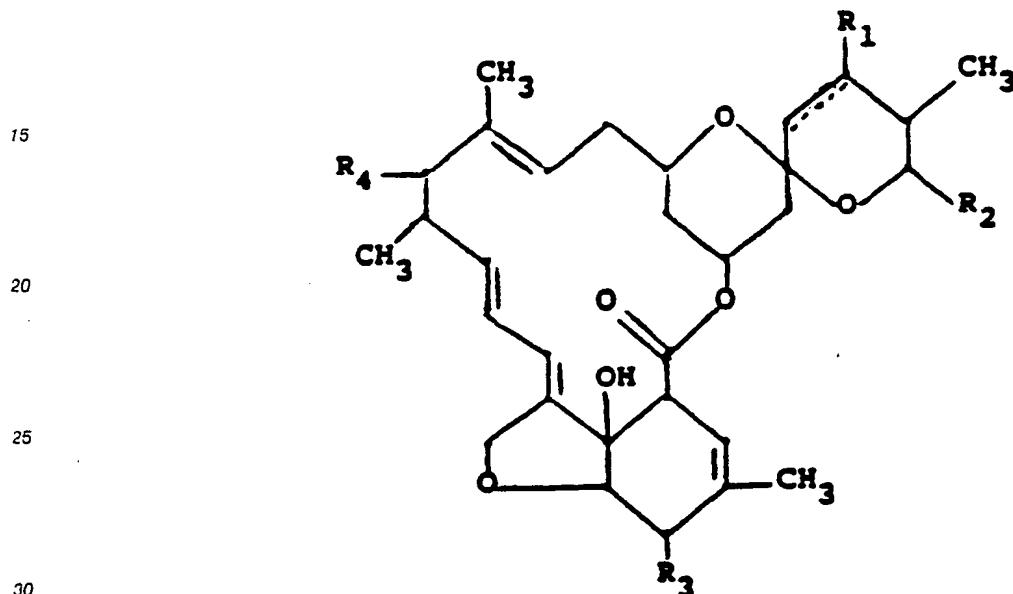
Avermectin compounds have been discovered to significantly reduce or eliminate the toxic effects upon 50 grazing animals, particularly ruminants, when tall fescue infected with fungi is ingested. The avermectin compounds are a series of compounds derived from the original avermectin natural products isolated from a fermentation broth and described in U.S. Patent 4,310,519 to Albers-Schonberg et al. The avermectins are isolated as four pairs of compounds and the pair identified as B1a/B1b is the most preferred. The preferred 22,23-dihydro derivatives of the avermectins are disclosed in 4,199,569 to Chabala et al. and the 22,23-dihydro avermectin B1a/B1b pair of compounds in an approximate 80:20 mixture are most preferred and are known as ivermectin.

Other avermectin derivatives are useful in preventing fescue toxicosis such as the monosaccharide and aglycone derivatives disclosed in U.S. Patent 4,206,205 to Mrozik et al; the acylated derivatives thereof such as those disclosed in U.S. Patent 4,201,861 to Mrozik et al; the 13-deoxy aglycone compounds disclosed in Re 32034 and Re 32006 to Chabala et al; and the 4'-keto and 4"-amino compounds disclosed in U.S. Patent 4,427,663 to Mrozik.

5 Additional compounds usable as in preventing fescue toxicosis are the milbemycin compounds disclosed in U.S. Patent 3,950,360 to Aoki et al. and the oxime derivatives thereof disclosed in U.S. Patent 4,547,520 to Ide et al.

The preferred avermectin compounds for use in preventing fescue toxicosis are realized in the following

10 structural formula:



wherein the broken line indicates a single or double bond;

15 R_1 is H, =O, loweralkanoyloxy or OH, provided that R_1 is present only when the broken line indicates a single bond;

R_2 is methyl, ethyl, isopropyl or sec-butyl;

R_3 is OH, OCH_3 or loweralkanoyloxy;

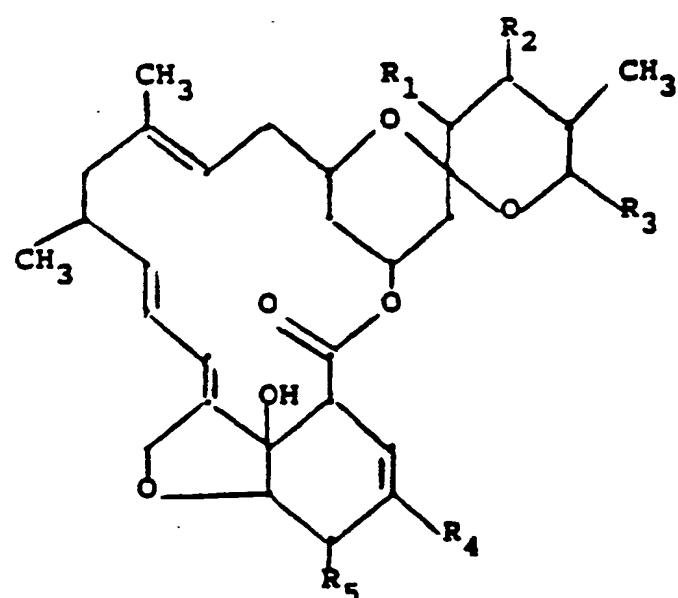
20 R_4 is H, OH, loweralkanoyloxy, α -L-oleandrosyloxy, 4'-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4'-loweralkanoyl- α -L-oleandrosyloxy, 4"-loweralkanoyl-4'-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4"-amino-4'-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4"-mono- or diloweralkylamino-4'-(α -L-oleandrosyl)- α -L-oleandrosyloxy, and physiologically acceptable salts thereof.

25 The preferred milbemycin compounds for use as growth promotion agents are realized in the following formula:

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wherein the various R groups have the following meanings:

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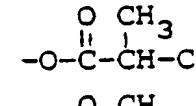
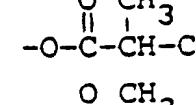
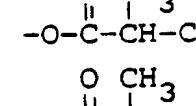
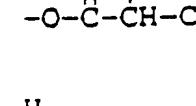
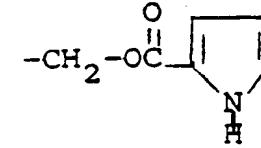
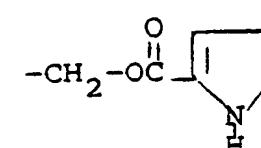
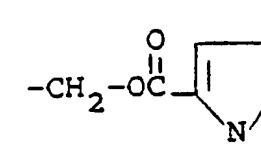
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| | R_1 | R_2 | R_3 | R_4 | R_5 |
|----|-------|-------|---|--|--------------------|
| 5 | H | H | CH ₃ | CH ₃ | OH |
| | H | H | CH ₃ | CH ₃ | OCH ₃ |
| | H | H | C ₂ H ₅ | CH ₃ | OH |
| 10 | H | H | C ₂ H ₅ | CH ₃ | OCH ₃ |
| | OH | |  | CH ₃ | OH |
| 15 | OH | |  | CH ₃ | OCH ₃ |
| | OH | |  | CH ₃ | OH |
| 20 | OH | |  | CH ₃ | OCH ₃ |
| 25 | H | H | CH ₃ |  | OH |
| 30 | H | H | C ₂ H ₅ |  | OH |
| 35 | H | H | i-C ₃ H ₇ |  | OH |
| 40 | H | H | CH ₃ | CH ₃ | =N-OR ₆ |
| | H | H | C ₂ H ₅ | CH ₃ | =N-OR ₆ |
| | H | H | i-C ₃ H ₇ | CH ₃ | =N-OR ₆ |

45 wherein R_6 is hydrogen or loweralkyl.

The term "loweralkyl" when used in the instant application is intended to represent those alkyl groups either straight or branched chain which have from 1-5 carbon atoms. Examples of such alkyl groups are methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, pentyl, and the like.

50 The term "loweralkanoyl" is intended to include those alkanoyl groups containing from one to five carbon atoms in either a straight or branched chain. Examples of such alkanoyl groups are formyl, acetyl, propionyl, butyryl, valeryl, and the like.

55 The "b" compounds, those with a 25-isopropyl group, are often not separated from the closely related "a" compounds with a 25-sec-butyl group since the physical and chemical properties of such compounds are similar, and as such the compounds are generally isolated as mixtures of the two compounds. Thus references in the instant application to "a" compounds such as B1a, A1a, and the like, are construed to define the pure compound as well as those which actually contain a certain proportion of the corresponding "b" compound. Alternatively, this representation of a mixture is sometimes done by referring to the

compounds without designating "a" or "b" such as in the A1 or B2 compounds, or by separating the "a" compound from the "b" compound by a slash (/) such as B1a/B1b, B2a/B2b and the like.

The avermectin compounds can be used to prevent and treat the effects of fescue toxicosis in ruminant and non-ruminant animals such as sheep, cattle, goats, horses, that are pastured in fields of tall fescue. The active compound can be fed to the animal by incorporating it into the animal's feed or drinking water or it can be administered in a unit dosage form either orally as a drench, tablet, bolus or sustained release bolus or parenterally by injection or from a subcutaneous implant, or by a topically applied solution or suspension. The administration of the active compounds will allow the animal to fully utilize the nutritional content of tall fescue, generally considered to be nutritionally adequate for maintenance and growth, without any of the manifestations of fescue toxicosis such as "fescue foot", "bovine fat necrosis" summer slump" and the like.

The active compounds can be administered to the animals at daily rates of from 0.004 to 2.0 mg/kg of body weight which may vary depending upon the particular animal being treated as well as the age and general physical condition of the animal. Preferably, daily dosages of from 0.04 to 1.0 mg/kg are utilized. When administered as part of the animal's feed or drinking water the active compound is present at rates of from 0.1 to 100 ppm which is determined to provide the appropriate daily amounts of the growth promotant compound.

The effects of an avermectin compound (ivermectin) in preventing symptoms of fescue toxicosis have been observed in field trials of cattle grazing on tall fescue highly infected (85%) with an endophytic fungus. The control animals showed classic signs of fescue toxicosis, reduced weight gain, poor coats, heat 20 intolerance, fever and the like. The treated animals were given a sustained release bolus prior to grazing containing sufficient ivermectin for 120 days at from 0.04 to 0.06 mg/kg per day. The treated cattle gained an average of 39.6 kg more than the untreated cattle and further did not show any signs of fescue toxicosis. By visible examination, the treated cattle could be distinguished from the untreated cattle by observing their larger size, better coat and better disposition. In addition, the treated cattle had better appetites than the 25 untreated cattle and grazed for longer periods of time, particularly in warmer weather when the effects of heat intolerance were becoming more apparent in the untreated cattle.

The test demonstrates the significant effects ivermectin and other avermectin and milbemycin compounds have on the elimination of the symptoms of fescue toxicosis.

In a further test, cattle were grazed on paddocks of tall fescue with high levels of endophyte fungal 30 infection. After 120 days the cattle continuously treated with ivermectin from a sustained release bolus gained an average of 28 kg more than the untreated cattle; about one-quarter of a kilogram per day over the controls. In this test the control cattle had a very low level parasite burden, thus any weight gains not observed would have to be due to fescue toxicosis, thus demonstrating the efficacy of the instant compounds in preventing toxic effects of such infected grasses.

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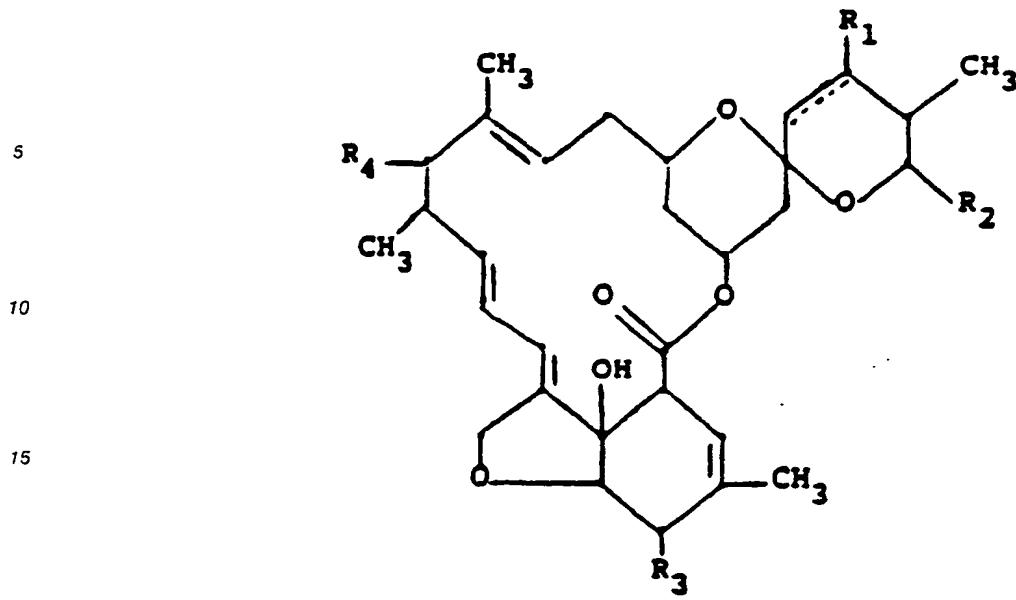
Claims

1. The use of an avermectin or a milbemycin compound, for the preparation of a treatment useful for 40 preventing fescue toxicosis in animals ingesting tall fescue.
2. The use as claimed in Claim 1 wherein the active compound has the formula:

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55



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wherein the broken line indicates a single or double bond;

R₁ is H, =O, loweralkanoyloxy or OH, provided that R₁ is present only when the broken line indicates a single bond;

25 R₂ is methyl, ethyl, isopropyl or sec-butyl;

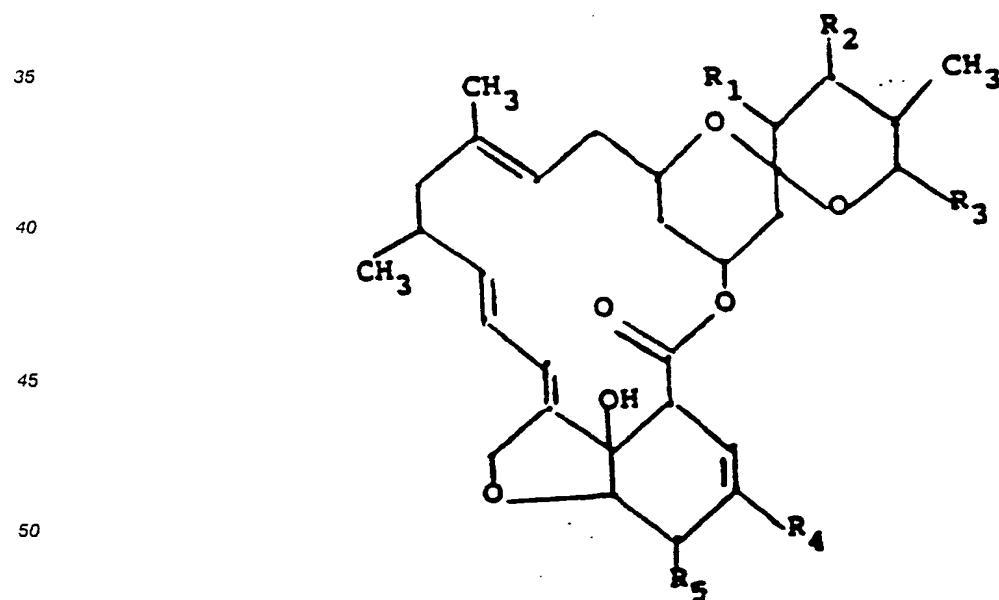
R₃ is OH, OCH₃ or loweralkanoyloxy;

R₄ is H, OH, loweralkanoyloxy, α -L-oleandrosyloxy, 4'-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4'-loweralkanoyl- α -L-oleandrosyloxy, 4"-loweralkanoyl-4'-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4"-amino-4-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4"-mono- or diloweralkylamino-4-(α -L-oleandrosyl)- α -L-oleandrosyloxy,

30 and physiologically acceptable salts thereof.

3. The use as claimed in Claim 2 wherein the active compound is invermectin.

4. The use as claimed in Claim 1 wherein the active compound has the formula:



55 wherein the compounds are determined when R₁, R₂, R₃, R₄ and R₅ have the following meanings:

| | R_1 | R_2 | R_3 | R_4 | R_5 |
|----|-------|--|------------|--|-----------|
| 5 | H | H | CH_3 | CH_3 | OH |
| | H | H | CH_3 | CH_3 | OCH_3 |
| | H | H | C_2H_5 | CH_3 | OH |
| | H | H | C_2H_5 | CH_3 | OCH_3 |
| 10 | OH | $O \begin{matrix} CH_3 \\ \\ -O-C-CH-C_4H_9 \end{matrix}$ | CH_3 | CH_3 | OH |
| | OH | $O \begin{matrix} CH_3 \\ \\ -O-C-CH-C_4H_9 \end{matrix}$ | CH_3 | CH_3 | OCH_3 |
| | OH | $O \begin{matrix} CH_3 \\ \\ -O-C-CH-C_4H_9 \end{matrix}$ | C_2H_5 | CH_3 | OH |
| | OH | $O \begin{matrix} CH_3 \\ \\ -O-C-CH-C_4H_9 \end{matrix}$ | C_2H_5 | CH_3 | OCH_3 |
| 15 | H | H | CH_3 | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| | H | H | C_2H_5 | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| 20 | H | H | CH_3 | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| | H | H | $i-C_3H_7$ | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| 25 | H | H | C_2H_5 | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| | H | H | $i-C_3H_7$ | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| 30 | H | H | CH_3 | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| | H | H | C_2H_5 | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| 35 | H | H | $i-C_3H_7$ | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | OH |
| | H | H | CH_3 | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | $=N-OR_6$ |
| 40 | H | H | C_2H_5 | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | $=N-OR_6$ |
| | H | H | $i-C_3H_7$ | $-CH_2-OC-\begin{array}{c} O \\ \\ \text{Cyclopentylidene} \\ \\ \text{NH} \end{array}$ | $=N-OR_6$ |

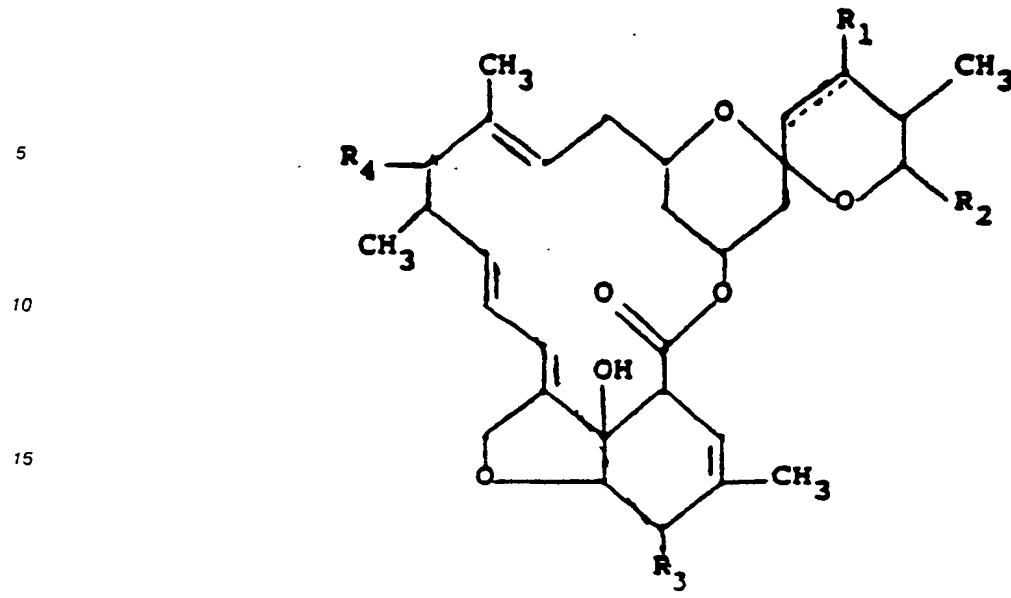
45 wherein R_6 is hydrogen or loweralkyl.

5. The use as claimed in Claim 1 wherein the active compound is administered in the animal's feed or drinking water.

6. The use as claimed in Claim 1 wherein the active compound is orally administered in a unit dosage form selected from a drench, tablet, bolus or sustained release bolus.

50 7. A composition useful for preventing fescue toxicosis in animals grazing on tall fescue which comprises an inert ingredient and an avermectin or milbemycin compound.

8. The composition of Claim 7 wherein the active compound has the formula:



20

wherein the broken line indicates a single or double bond;

R₁ is H, =O, loweralkanoyloxy or OH, provided that R₁ is present only when the broken line indicates a single bond;

25 R₂ is methyl, ethyl, isopropyl or sec-butyl;

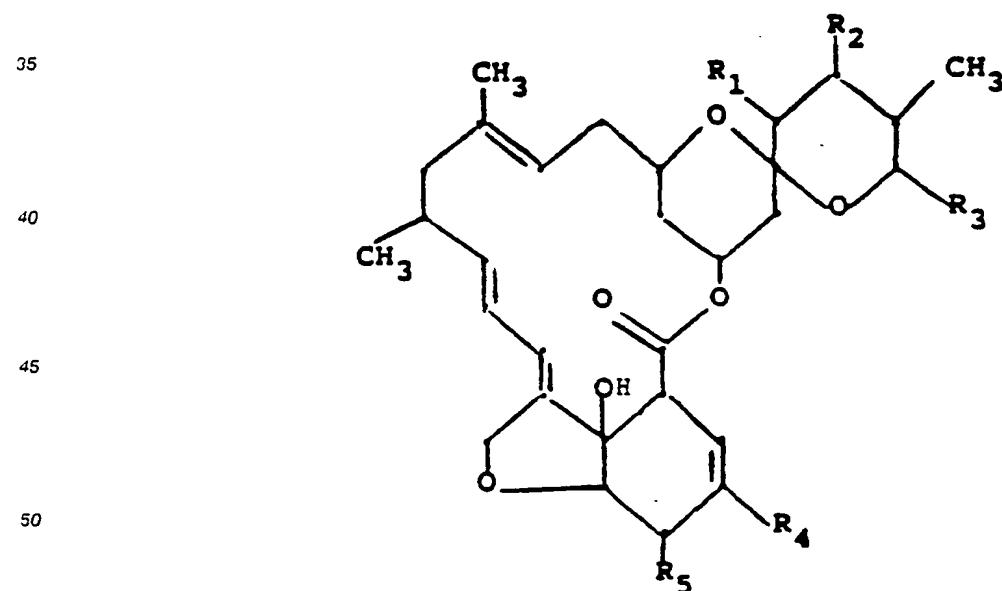
R₃ is OH, OCH₃ or loweralkanoyloxy;

R₄ is H, OH, loweralkanoyloxy, α -L-oleandrosyloxy, 4'-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4'-loweralkanoyl- α -L-oleandrosyloxy, 4'-loweralkanoyl-4'-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4"-amino-4-(α -L-oleandrosyl)- α -L-oleandrosyloxy, 4"-mono- or diloweralkylamino-4-(α -L-oleandrosyl)- α -L-oleandrosyloxy,

30 and physiologically acceptable salts thereof.

9. The composition of Claim 8 wherein the active compound is ivermectin.

10. The composition of Claim 7 wherein the active compound has the formula:



55 wherein the compounds are determined when R₁, R₂, R₃, R₄ and R₅ have the following meanings:

| | R_1 | R_2 | R_3 | R_4 | R_5 |
|----|-------|---|---------------------------------|--|--------------------|
| 5 | H | H | CH ₃ | CH ₃ | OH |
| | H | H | CH ₃ | CH ₃ | OCH ₃ |
| | H | H | C ₂ H ₅ | CH ₃ | OH |
| | H | H | C ₂ H ₅ | CH ₃ | OCH ₃ |
| 10 | OH | $\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ -\text{O}-\text{C}-\text{CH}-\text{C}_4\text{H}_9 \end{array}$ | | CH ₃ | OH |
| | OH | $\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ -\text{O}-\text{C}-\text{CH}-\text{C}_4\text{H}_9 \end{array}$ | | CH ₃ | OCH ₃ |
| 15 | OH | $\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ -\text{O}-\text{C}-\text{CH}-\text{C}_4\text{H}_9 \end{array}$ | | CH ₃ | OH |
| | OH | $\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ -\text{O}-\text{C}-\text{CH}-\text{C}_4\text{H}_9 \end{array}$ | | CH ₃ | OCH ₃ |
| 20 | OH | $\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ -\text{O}-\text{C}-\text{CH}-\text{C}_4\text{H}_9 \end{array}$ | | CH ₃ | OH |
| | OH | $\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ -\text{O}-\text{C}-\text{CH}-\text{C}_4\text{H}_9 \end{array}$ | | CH ₃ | OCH ₃ |
| 25 | H | H | CH ₃ | $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CH}_2-\text{OC}-\text{C}_5\text{H}_4\text{N} \\ \parallel \\ \text{H} \end{array}$ | |
| | H | H | C ₂ H ₅ | $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CH}_2-\text{OC}-\text{C}_5\text{H}_4\text{N} \\ \parallel \\ \text{H} \end{array}$ | |
| 30 | H | H | i-C ₃ H ₇ | $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CH}_2-\text{OC}-\text{C}_5\text{H}_4\text{N} \\ \parallel \\ \text{H} \end{array}$ | |
| | H | H | CH ₃ | $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CH}_2-\text{OC}-\text{C}_5\text{H}_4\text{N} \\ \parallel \\ \text{H} \end{array}$ | |
| 35 | H | H | C ₂ H ₅ | $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CH}_2-\text{OC}-\text{C}_5\text{H}_4\text{N} \\ \parallel \\ \text{H} \end{array}$ | |
| | H | H | i-C ₃ H ₇ | $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CH}_2-\text{OC}-\text{C}_5\text{H}_4\text{N} \\ \parallel \\ \text{H} \end{array}$ | |
| | H | H | CH ₃ | $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CH}_2-\text{OC}-\text{C}_5\text{H}_4\text{N} \\ \parallel \\ \text{H} \end{array}$ | |
| 40 | H | H | C ₂ H ₅ | CH ₃ | =N-OR ₆ |
| | H | H | i-C ₃ H ₇ | CH ₃ | =N-OR ₆ |
| | H | H | CH ₃ | CH ₃ | =N-OR ₆ |

45 wherein R_6 is hydrogen or loweralkyl.

- 46 11. The composition of Claim 7 which is topically or orally administered.
12. The composition of Claim 11 which is a medicated feed or drinking water.
13. The composition of Claim 11 which is a unit dosage formulation selected from a drench, tablet, bolus or sustained release bolus.
14. The composition of Claim 7 which is parenterally administered.
- 50 15. The composition of Claim 14 which is a subcutaneous implant.



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㉔ Date of publication of application:
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㉗ Prevention of fescue toxicosis in grazing animals.

㉗ There is disclosed a method for the prevention of fescue toxicosis in grazing animals. Fescue toxicosis results from a grazing animal ingesting certain toxins present in or on the grass which can impair growth, reproductive performance, and is sometimes fatal. It has been discovered that the administration of ivermectin or related avermectin compounds is effective in reducing or eliminating the toxic effects of fescue endophyte ingestion.

EP 0 311 195 A3



| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|--|--|---|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl. 4) |
| X | JP-A-62 221 691 (GLAXO GROUP LTD) * Claims 1,8; page 5, lines 18-21; page 6, lines 4-9; page 6, line 15 - page 9, line 2 * & EP-A-241 145 (GLAXO GROUP LTD) (Cat. P) --- | 1,5-8, 11-15 | A 23 K 1/17 A 01 N 43/90 A 61 K 31/70 C 07 D 493/22 C 07 H 19/01 |
| X | THE JOURNAL OF ANTIBIOTICS, vol. 37, no. 3, 1984, pages 253-259, Tokyo, JP; P.H. CALCOTT et al.: "Inhibition of chitin metabolism by avermectin in susceptible organisms" * Page 253, abstract; page 254: "Bioassays"; page 255, table 1; page 256, table 2; pages 257-258: "Discussion" * --- | 1,7 | |
| D,A | US-A-4 427 663 (HELMUT H. MROZIK) * Column 13, lines 5-25 * ----- | 1 | |
| TECHNICAL FIELDS SEARCHED (Int. Cl.4) | | | |
| A 23 K A 61 K C 07 H C 07 D A 01 N | | | |
| The present search report has been drawn up for all claims | | | |
| Place of search | Date of completion of the search | Examiner | |
| THE HAGUE | 30-07-1990 | DEKEIREL M.J. | |
| CATEGORY OF CITED DOCUMENTS | | T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document | |
| X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document | | | |